Remarks

Claims 35-37, 39 and 57-94 are pending in the subject application. By this Amendment, Applicants have canceled claims 35-37, 39 and 57-94 and added new claims 95-138. Support for the new claims can be found throughout the subject specification and in the claims as originally filed and previously presented (the claims have been revised to indicate SEQ ID NOs: for the peptides previously claimed and pages 14-16 of the as-filed specification). Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 95-138 are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

As an initial matter, Applicants note that the previous After Final amendment was not entered in this matter. Entry of the amendments and arguments presented therein is respectfully requested.

Claims 35-37, 39 and 57-94 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Office Action indicates that previously submitted arguments were not found persuasive and states that adequate written description is conferred by correlation between structure and function. The Office Action further argues that the claims are drawn to a genus of polypeptides that are defined by their functionality and that fusion proteins, active mutants and peptides of between 5 and 10 amino acids that bind OX40R do not have adequate written description. While the rejection is now moot in view of the cancellation of claims 35-37, 39 and 57-94, Applicants traverse the rejection as it may be applied to the newly presented claims.

At the outset, Applicants note that each of the polypeptides that are alleged to lack adequate written description are defined by both structure and function within the claims. For example, claim 95 recites:

An isolated polypeptide consisting of:

a) SEQ ID NO: 6;

b) SEQ ID NO: 6, wherein one or more amino acids have been deleted, said polypeptide contains SEQ ID NO: 13 and said polypeptide binds to the OX40 receptor (OX40R);

c) between 5 and 10 contiguous amino acids of SEQ ID NO: 1, wherein said polypeptide contains SEQ ID NO: 13 and binds to OX40R;

d) SEQ ID NO: 8 or SEQ ID NO: 13;

e) an active mutant of a), b), c) or d), wherein one or more of the amino acids has been conservatively substituted and said active mutant binds to OX40R;

f) a fusion polypeptide or peptide comprising a protein sequence other than human OX40L fused to:

i) SEQ ID NO: 6;

ii) SEQ ID NO: 6, wherein one or more amino acids have been deleted, said polypeptide contains SEQ ID NO: 13 and said polypeptide binds to the OX40 receptor (OX40R);

iii) between 5 and 10 contiguous amino acids of SEQ ID NO: 1, wherein said polypeptide contains SEQ ID NO: 13 and binds to OX40R; or

iv) SEQ ID NO: 8 or SEQ ID NO: 13; or

g) a derivative of a), b), c), d), e) or f).

As will be noted from the claims, each of the claim subparts recite peptides that have structural limitations or both structural and functional limitations. For example, subpart c) recites a peptide consisting of between 5 and 10 contiguous amino acids of SEQ ID NO: 1, wherein said polypeptide contains SEQ ID NO: 13 and binds to OX40R. Thus, it is respectfully submitted that adequate written description of such a peptide exists in the as-filed specification. Likewise, fusion proteins containing such a peptide also have adequate written description.

With respect to derivatives of the claimed polypeptides, it is respectfully submitted that these peptides are adequately described. For example, derivatives are defined at page 14 and refer "to derivatives which can be prepared from the functional groups present on the lateral chains of the amino acid moieties or on the N-/ or C-terminal groups according to known methods. Such derivatives include for example esters or aliphatic amides of the carboxyl-groups and N-acyl derivatives of free amino groups or O-acyl derivatives of free hydroxyl-groups and are formed with

acyl-groups as for example alcanoyl- or aroyl-groups". Thus, it is respectfully submitted that the as-filed specification and claims conform to the written description requirement of section 112.

Finally, the Office Action argues that active mutants of the claimed polypeptides are not supported by the as-filed specification. In this regard, Applicants respectfully traverse. The as-filed specification indicates that the OX40R binding portion of the disclosed peptides is associated with amino acids 107-111 of SEQ ID NO: 13 (see Example 2, page 36, lines 11-15 and Figure 6). Further, the as-filed specification discloses a number of peptides having the recited characteristics (see Example 2) and the as-filed specification (at pages 9-10) provides teaching as to substitutions that can be made within the claimed peptides and methods of screening the peptides for activity (OX40R binding). Applicants also note that the term "active" is defined in the as-filed specification as a compound demonstrating the OX40R binding properties of the peptides disclosed within the as-filed application (see page 9, lines 9-10). Applicants further note that the claims indicate that the active mutants of the claimed polypeptides must also bind to OX40R and that the amino acid substitutions are to be made are also specified. Thus, it is respectfully submitted that the claimed polypeptides are defined both structurally and functionally and that adequate written description of the claimed polypeptides was provided in the as-filed specification. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Claims 35-37, 39 and 57-94 are rejected under 35 U.S.C. § 112, second paragraph, as indefinite. The Office Action argues that it is unclear as to whether the phrase "one or more" may include a situation in which all the amino acids may be substituted. Applicants respectfully submit that the claims are definite and that one skilled in the art, in view of the teachings of the as-filed specification, would be able to ascertain the metes and bounds of the claimed invention (see, for example, page 9, lines 11-17). Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, is respectfully requested.

Claims 35-37, 39 and 57-94 are rejected under 35 U.S.C. § 103(a) as obvious over Godfrey *et al.* (U.S. Patent No. 6,242,566) in view of Chien *et al.* (1991). The Office Action asserts that Godfrey *et al.* teach purified ACT-4-L ligand polypeptides; an exemplified ACT-4-L ligand designated ACT-4-l-h-1. In addition, it is stated that Godfrey *et al.* teach purified extracellular domains of ACT-4-L ligands. The Office Action cites Chien *et al.* as teaching a method by which a

protein-protein interaction is indentified in vivo through reconstitution of the activity of a transcriptional activator. Applicants note that the Office Action also asserts that the claimed invention is obvious and that one skilled in the art would have arrived at the domains essential to the binding of ACT 4L to its receptor because the domain to be searched was disclosed by Godfrey *et al.*, the search would have entailed a finite number of fragments already envisioned (in length). Applicants respectfully traverse the rejection and submit that a *prima facie* case of obviousness has not been established by the Patent Office.

At the outset, Applicants note that the obviousness rejection of record appears to rely on the rationale articulated in *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727 (2007) in establishing the rejection of record. Applicants also note that the Patent Office's guidelines promulgated in light of the KSR decision also provide a similar rationale for establishing an obviousness rejection (see 72 Fed. Reg. 57526, 57532). Applicants further note that the full quote of that portion of the KSR decision which appears to serve as the basis of the instant rejection states that "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103." Further, the Patent Office guidelines state (at page 57532):

> E. "Obvious To Try"—Choosing From a Finite Number of Identified, Predictable Solutions, With a Reasonable Expectation of Success
>
> To reject a claim based on this rationale, Office personnel must resolve the *Graham* factual inquiries. Office personnel must then articulate the following:
>
> (1) a finding that at the time of the invention, there had been a recognized problem or need in the art, which may include a design need or market pressure to solve a problem;
> (2) a finding that there had been a finite number of identified, predictable potential solutions to the recognized need or problem;
> (3) a finding that one of ordinary skill in the art could have pursued the known potential solutions with a reasonable expectation of success; and

> (4) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.

In this case, Applicants respectfully submit that the Patent Office has failed to establish the *prima facie* obviousness of the claimed invention as the rejection of record fails to meet the requirements of either the KSR decision or the guidelines promulgated by the Patent Office. Namely, the Patent Office has failed to establish that there was a recognized problem or need in the art to solve a problem that would have motivated one to even try to identify peptides corresponding to those claimed in this matter. Further, the Patent Office has failed to establish that there were a finite number of identified, predictable solutions for solving the recognized need or problem. It is noted that the Office Action argues that there are a finite number of peptide fragments that can be generated in light of the teachings of Godfrey *et al.*; however, it is clear that thousands or tens of thousands of possible fragments could be generated from the 133 amino acid extracellular domain of the OX40L and no finding as to which of those fragments would have predictably solved the problem (which is, as of yet, unidentified by the Patent Office) has been made.

It is further submitted that a *prima facie* case of obviousness has not been established as it is unclear that one skilled in the art would have had a reasonable expectation of success in arriving at the claimed invention on the basis of the cited references. For example, the as-filed specification indicates (at page 2) that:

> OX40L interacts with OX40R as a homotrimer with a high affinity (Kd = 0.2-0.4 nM), and various binding assays have been tested on this system (Taylor L et al, 2002; Taylor L and Schwartz H, 2001; Al-Shamkhani A et al., 1997). However, no tridimensional structure has been solved so far, neither detailed structure-activity studies have been performed, in order to provide any further molecular details on the mechanism of OX40L-OX40R interaction.

Thus, the as-filed specification indicates that it is unknown whether OX40L interacts with its cognate receptor via a linear peptide or via a conformational arrangement of the homotrimer and the cited combination of references provides no teaching as to why one of skill in the art, in view of such a recognition, would have had a reasonable expectation of identifying linear peptides having the ability to bind to OX40R and antagonize its activity.

Applicants further note that only large molecules, such as the extracellular domain of OX40L or antibodies that bind to OX40R were recognized in the art as being effective OX40R binding agents (see paragraph bridging pages 3-4 of the as-filed specification) and that the majority of these agents were recognized to be agonists of OX40R. This recognition, too, would not have led one skilled in the art to expect that small linear peptides would have had the ability to bind to OX40R and antagonize the activity of the receptor and/or its interaction with OX40L.

Additionally, the claimed peptides exhibit a greater ability to inhibit (antagonize) the interaction between OX40L and OX40R as compared to a control (using the AlphaScreen technology described in Example 1). In this regard, Applicants attach a comparative table demonstrating that all peptides within the extracellular domain of OX40L did not exhibit a higher affinity to OX40R in the AlphaScreen Assays presented in Example 2. The data in this table is found throughout the as-filed specification (support for the binding tests results now provided in tabular form can be found in the as-filed specification as indicated in the last three columns of the Table). As is apparent from the Table, only the claimed peptides, all sharing the core amino acid sequence of SEQ ID NO: 13, exhibit the ability to act as OX40L antagonists and block the interaction of OX40L with OX40R. Accordingly reconsideration and withdrawal of the rejections under 35 U.S.C. § 103(a) is respectfully requested as a *prima facie* case of obviousness has not been established in this matter.

It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position. Applicants expressly reserve the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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FCE/sl
Attachment: Comparative Table

Original Table III completed with the binding abilities of the different peptides (based on AlphaScreen Assays presented in the specification and example 2 and Figures 5 and 6)

Peptide name	Peptide sequence	Correspondance with human OX40L	Ability to inhibit OX40R-OX40L interaction	Results of the binding tests (support: Table III +)		
P1 (SEQ ID NO:2)	VASLTYKDKVYLNVTTDNTSLDDFHVNGGEL	150-180	0	Fig. 5A + From l.18 p.35 to l.2 p.36		
P2 (SEQ ID NO:3)	LDDFHVNGGELILIHQNPGEFCVL	160-183	0	Fig. 5A + From l.18 p.35 to l.2 p.36		
P3 (SEQ ID NO:4)	VSHRYPRIQSIKVQFTEYKKEKGFILTSQ	52-80	0	Fig. 5A + From l.18 p.35 to l.2 p.36		
P4 (SEQ ID NO:5)	EKGFILTSQKEDEIMKVQNNSVIINCDGFYL	72-102	0	Fig. 5A + From l.18 p.35 to l.2 p.36	Fig. 5B	
P5 (SEQ ID NO:6)	IINCDGFYLISLKGYFSQEVNISLHYQKDEE	94-124	+	Fig. 5A + From l.18 p.35 to l.2 p.36	Fig. 5B	
P6 (SEQ ID NO:7)	HYQKDEEPLFQLKKRSVNSLMVASLTYKDK	118-148	0	Fig. 5A + From l.18 p.35 to l.2 p.36		
P5-1 (SEQ ID NO:8)	GYFSQEVNIS	107-116	+			Fig.6A,B p.36 l.3-10
P5-2 (SEQ ID NO:9)	ISLHYQKDEE	107-124	0			Fig.6A,B p.36 l.3-10
P5-3 (SEQ ID NO:10)	GFYLISLKGY	99-108	0			Fig.6A,B p.36 l.3-10
P5-4 (SEQ ID NO:11)	QEVNISLHYQ	111-120	0			Fig.6A,B p.36 l.3-10
P5-5 (SEQ ID NO:12)	IINCDGFYLI	94-103	0			Fig.6A,B p.36 l.3-10
P5-1a (SEQ ID NO.13)	GYFSQ	107-111	+			p.36 l.11-15

0 = similar than control
+ = higher affinity (micromolar range) than control